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# The Eleanor & Lou Gehrig MDA/ALS Research Center at Columbia University

**This issue of the Eleanor and Lou Gehrig MDA/ALS Newsletter is dedicated to the courage and strength demonstrated by:** Agripina Abreu, Christopher Ambler, Gary Baker, Fred Berger, Herman Berlin, Vanessa Brown, Manfred Borstelmann, James Burckhardt, Constance Burke, Olga Cabrera, Laura Campana, Joseph Capuano, Estelle Cassara, Martin Cavanagh, Ann Marie Cimmino, Verona Cobbs, Irwin Cohen, Lewis Cole, Dominick Costa, Max Daverman, Maria DeCastro, Richard Diego, Julia Digirolamo, Yvonne Douse, William Drucker, Denis Galle, David Garbar, Linda Gold *(continued on page 2)*

## From the desk of Hiroshi Mitsumoto, MD

Dear Friends,

Unfortunately, we missed out on producing a few of our newsletters during this past winter, but we are glad to share with you that we are now fully back in business! In this Summer 2009 edition, I would like to bring you up to date on some new breakthroughs in understanding ALS, as well as tell you about our ALS center operation.

As you know, approximately 5% to 10% of all ALS cases are familial or hereditary; that is, ALS caused by certain gene mutations in specific DNA. Mutations in the DNA encoding the enzyme, called superoxide dismutase 1 (SOD1), result in approximately 20% of all familial ALS cases. The discovery of SOD1 mutations in 1993 was considered to be one of the most important steps in the progress of understanding ALS. For the past 15 years, a majority of the basic, translational and drug discovery research efforts have been accomplished by using SOD1 rodent models, often called the ALS model. Since the SOD1 mutation only accounts for a small amount of ALS cases, some individuals are concerned about the apparent limitation of SOD1 models; nevertheless, they are still the best models available.

Over the past few years, there has been another major breakthrough for understanding the neurodegenerative process of motor neurons in ALS. It has been discovered that, in ALS patients, the protein called TDP-43 (Tar-DNA-binding protein-43), turns abnormal and is tagged by a digestive protein called ubiquitin. This ubiquitinated TDP-43 protein, which is normally found only inside of the cell

nucleus (the genetic commanding center of the cell), is instead found outside of the nucleus in people with ALS. This abnormal protein is aggregated and forms protein conglomerates, often called cell inclusion bodies, which are found in ALS motor neurons. In fact, such inclusion bodies are now found in many types of ALS, including sporadic ALS, non-SOD1-linked ALS, Guamanian ALS, and ALS with frontotemporal dementia. They are not found in familial ALS with SOD1 mutations (at best still debated), nor in animal models of SOD1 mutations. Therefore, TDP-43 has become tremendously important in understanding the disease mechanisms of ALS. Furthermore, another exciting report came out only a few months ago in which new mutations in the FUS gene were found in a few percent of patients with familial ALS. Slowly but surely, investigators are dissecting out the causes of familial ALS and the breakthroughs involving the TDP-43 protein and the FUS gene are significant steps in this process.

The most extraordinary implication of the FUS and TDP-43 findings is that the FUS and TDP-43 proteins are classified into DNA/RNA-binding proteins that control the RNA metabolism inside the nucleus. When I was a medical student (a few decades ago!), I learned that the DNA code to generate a protein is transferred to RNA, and then the RNA template will lead to a protein. The reality is far more complex. In ALS, it appears that there is some complicated derangement in the DNA and RNA metabolism, resulting in the production of abnormal proteins. *(continued on page 2)*





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This is clearly highly worthwhile to study extensively in the future.

It turns out that the more we know about the cause of ALS, through scientific breakthroughs or our own studies, the more we realize that there are likely multiple causes. We strongly believe that the secret to understanding ALS lies within ALS patients themselves. The investigation of patients with ALS is essential to finding the cause and cure of this seemingly impossible disease. For this reason, we are deeply grateful to those who are willing to participate in our studies.

I would also like to tell you about our ALS Center operation in relation to other ALS Centers across the United States. Currently, there are more than 70 centers; about half of them are funded/supported by the Muscular Dystrophy Association (MDA) and the other half are funded/supported by the ALS Association (ALSA). There is a common misconception that MDA only supports muscular dystrophy, while in fact, they support more than 40 neuromuscular diseases, ALS being one of their key diseases and one they place a strong emphasis on. Our Center, as indicated in its name, the Eleanor and Lou Gehrig MDA/ ALS Research Center, is solely funded by the MDA and we are extremely grateful to have their support. However, I must tell you, make no mistake about it- the funds and support we receive are insufficient to run our center. As you can imagine, a team of clinicians - such as dietitians, speech pathologists, physical therapists, psychologists, and clinical nurses- who evaluate and provide care for the patients is expensive and may cost \$1,000 per patient. Yet, commercial insurances or Medicare only reimburse the physicians- not the other clinicians- for their time. The recent budget constraints posed by the Department and University have given us further limitation. So, although the MDA supports us, it is unfortunately not enough and I fear that the current multidisciplinary approach may be an endangered species in the recent medical care climate.

Despite our obvious obstacles, we are fully committed to providing state-of-the-art multidisciplinary care for all of the patients who visit us here. To assist us with this commitment, we encourage and are grateful for your strong support of our patient care and research activities. We have to work together as a team to help our ALS Center get through this difficult time.

Sincerely yours,

## **IPLEX: Fact and Fiction** **By Jinsy Andrews, MD and Hiroshi Mitsumoto, MD**

The internet is the 'information superhighway' and has become a primary source of information for most things today. Its role has grown in the ALS community and has become a way to share information, and communicate and advance research among patients, organizations and researchers. Much like the way lithium gained attention in the ALS community, recently IPLEX has received a lot of interest and attention on the internet and in the media.

IPLEX (or mecasermin rinfabate) is recombinant human insulin-like growth factor-1 (rhIGF-1) and binding protein 3 (IGFBP3), which is manufactured by Insmed. In the United States, it is FDA approved only for the treatment of growth failure in children due to IGF -1 deficiency. Although IPLEX is being studied in a phase II study for myotonic dystrophy, and in 'early studies' on retinopathy of prematurity and HIV-associated adipose redistribution syndrome (according to Insmed's website, [www.insmed.com](http://www.insmed.com)), the only information regarding ALS is the availability of IPLEX to Italian patients with ALS through the 'expanded access program' (EAP). The EAP came about after several Italian ALS patients petitioned the government for the drug based on their own experiences on IPLEX. Their success relied heavily on one particular patient whose diagnosis is questionable<sup>1</sup>.

Subsequently, a movement by the ALS community persuaded Insmed to manufacture IPLEX in limited supply through compassionate use. Initially, the FDA denied all applications for compassionate use. However, they reversed their decision after they received information regarding safety and experience in a limited number of ALS patients in Italy (although this data did not demonstrate a clear benefit in ALS).

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*(continued from p. 1)* Celia Goldhaber, Kathleen Groschadl, Rishi Grover, Eleanor Hanen, Veronica Hanlon, Syed Hussain, Rose Imperato, Arnold Jacobs, Riki Jacobs, Ellen James, Nikolas Karsos, Robert Keen, Susan Kirsch, Catherine Kleinpeter, Mark Kuhn, Virginia Lee, Dorothy Leide, Maureen Lozito, Anthony Magazzu, Patricia Majka, Michael Martirano, Harold Masback, Kathleen Matteis, Evelina Mendes, Jean Migneault, Victor Mion, Helen Mok, Damaris Ortega, Gerald O Sullivan, Millicent Price, Russell Prokop, Beryl Quinerly, Marvin Rasnick, Thomas Reilly, Sharon Rodney, Julia Russnow, Harry Salwen, Ann Saunders, Andrew Schemera, Zevie Schizer, John Scully, Dora Silveria, Pasquale Silvestri, Frank Stevens, Alice Solberg, Vera Terranova, Sidney Valo, Muriel Walter, Gloria Weiss, Dawn Whaley, Meda Whilby, Nigel White, and Sharon Wright. We apologize for any omissions.



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IGF-1 (the main ingredient of IPLEX) has been tried in several clinical trials in ALS. One trial showed a small effect in slowing disease progression when compared to placebo<sup>2</sup>. But two subsequent studies, one recently published in November of 2008, showed no benefit compared to placebo<sup>3,4</sup>. In 2006, IPLEX was given to a small number of ALS patients in Italy. At the time, Italian researchers were concerned about providing the medication and had called for a clinical trial, but lacked sufficient funding.

Although no objective data is available on the positive effects of IPLEX in ALS patients, it is fairly easy to find subjective reports in chat rooms, blogs, or even the local paper. The story of IPLEX began as several positive experiences from patients taking the drug snowballed to become many unsubstantiated reports of IPLEX being a 'miracle drug' (implying a cure) or 'the only medication to show benefit in ALS' (implying that there have been clinical trials). As the story evolves over time, it can be difficult to sort things out, but here are a few facts regarding IPLEX and ALS:

1. There are several anecdotal reports (not based on clinical trials) from patients of some improvement of symptoms.
2. There is very little preclinical and no human clinical data available at this time that shows a clear benefit of IPLEX in ALS (not even from the patients from Italy).
3. Although the drug is FDA approved for children, it is not commercially available in the US (which means that a script can't be written and taken to a pharmacy to obtain medication). Children with growth hormone deficiency get their medication through Tercica or Genentech, which is IGF without binding protein 3 and is commercially available. IPLEX was completely unavailable due to a law suit from patent infringement. If a patient wants IPLEX, they have to get it directly from Insmmed after IND and IRB approval.
4. The ideal dose of IPLEX in ALS and cost to patients is unclear.
5. The agreement among the drug companies (Insmmed, Tercica and Genentech) allowed access to IPLEX from Insmmed; however, each individual patient in the U.S. that wants access to the drug needs to go through a complex process of approval through the Food and Drug Administration and a separate approval through an institutional review board (IRB).
6. Currently there is no formal clinical trial being conducted in the US. Insmmed has reported working on plans for a clinical trial directly through them but no further information has been given.

Additionally, off label prescribing of 'promising'

medications in ALS has caused trouble in the past. For example, Minocycline, an FDA approved antibiotic, was tested in a government funded phase III clinical trial in ALS. Many patients who could not participate or did not want to participate in the trial requested an off label prescription of minocycline. However, results demonstrated worsening function in ALS patients who took minocycline in the formal clinical trial. This was a tough lesson learned and raised caution regarding off label prescription in ALS.

With all this said, IPLEX may still be a contender. An appropriate clinical trial must be performed to study safety and efficacy before we can justify the use of IPLEX in patients with ALS. Protein molecules of IGF-I and the receptors are too large to penetrate into the brain and spinal cord, which is the major limitation for these molecules to exert their effects in humans. Although the most recent IGF-1 trial was negative<sup>5</sup>, researchers in the U.S. continue to work on altering the structure of IGF-1 and to try different methods of delivery in hopes that it can still be used for therapy in ALS.

The internet has become a great tool for patients and researchers to share information quickly. But just as easily as information can be shared, it can also be easily misrepresented or taken out of context. Although the ALS community as a whole is in search of the 'miracle drug', it is important to keep the facts clear while remaining hopeful that effective therapy is out there. Our research center is always ready to participate in a scientifically-sound clinical trial with IPLEX. In the interim, we will provide the best multidisciplinary care for patients with this disease.

### References:

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4. Sorenson EJ, Windbank AJ, Madrekar JN, et al. Subcutaneous IGF-1 is not beneficial in two year ALS trial. *Neurology*, 2008; 71: 1770-1775.
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# The Eleanor and Lou Gehrig MDA/ALS Research Center

**CURRENT CLINICAL TRIALS**

**Actively Enrolling:**  
 -Ambispective case-control study of Oxidative Stress  
 -Non-Invasive Ventilation

**Ongoing (closed to enrollment):**  
 -Talampanel in ALS  
 -Lithium in Combination with Riluzole in ALS  
 -2-Part, Randomized, Double-Blind, Safety and Tolerability Study Evaluating KNS-760704 in Patients with ALS  
 -Dextromethorphan/Quinidine (DMQ) in the Treatment of Pseudobulbar Affect in ALS

**Upcoming:**  
 -Clinical Trial of Ceftriaxone in Subjects with ALS

**Completed:**  
 -Exercise and Oxidative Stress in ALS  
 -Stage II Early Treatment of ALS with Nutrition  
 -Genetic and Epidemiology Study  
 -Efficacy of Using Skin Cutometer Measurements as a Biomarker for the Progression of ALS  
 -Skin Biopsies for Generation of ALS-Specific Human Embryonic Stem Cells

Please visit our website at [www.columbiaals.org](http://www.columbiaals.org) for more information.



**Planned Giving**

The Eleanor and Lou Gehrig MDA/ALS Research Center at Columbia University is funded primarily through grant assistance and philanthropic donation. As a multidisciplinary clinic, our center is expensive to sustain, and compensation from the insurance companies is not sufficient. We value your friendship and support for ALS research and education. It is your contribution that allows us to maintain high quality patient care.

If you would like to contribute, please make your check payable to:  
 The ALS Gift Fund  
 Columbia University Medical Center  
 Eleanor and Lou Gehrig MDA/ALS Research Center  
 710 W. 168th Street, 9th Floor  
 New York, NY 10032

For more information on donations to our center, please contact Allison DiRienzo at 212-305-4746 or visit our website at [www.columbiaals.org](http://www.columbiaals.org).



## Non-invasive Ventilation

Non-invasive ventilation (NIV) is a breathing assistance strategy used to help people with ALS who have developed weakness of the breathing muscles. A small ventilator delivers pressurized air through a mask that fits over or into the nose, or over the nose and mouth. NIV is thought to be most protective and beneficial during sleep, when breathing naturally becomes shallower and more irregular, but many patients with ALS find that wearing it for periods during the day can give them some respite.

NIV is typically started when lung function, measured by the forced vital capacity (FVC), decreases to 50% of normal predicted values, or when symptoms of respiratory insufficiency, such as shortness of breath or frequent morning headaches, develop. Because it takes a while to get acclimated to using NIV, many patients try it out for an hour or two during the day initially, and subsequently progress to using it at night.

Some studies suggest that patients who are able to use NIV successfully (most nights of the week for at least 4 hours per night) during sleep enjoy prolonged survival and quality of life. However, no published study has looked at how effectively the NIV helps patients to ventilate (how much it supports breathing and maintains oxygen and carbon dioxide levels at normal values). We have been investigating this question by performing home sleep studies on ALS patients who report that they are successfully using NIV during sleep (at least 4 hours per night, at least 4 nights per week). Our preliminary results suggest that, in many patients who use NIV “successfully”, there is actually significant failure of ventilation or oxygenation during their sleep period. We continue to recruit patients for this important study.

We have also started to investigate whether intensive monitoring and adjustment of NIV with repeated home sleep studies can maintain quality of life, preserve lung function and prolong survival compared with the usual practice of adjusting NIV on the basis of symptoms alone. This is a 6-month trial enrolling ALS patients who are advised to start using NIV. Half of the patients will be assigned to the “standard of care” group, whereas the other half will be assigned to the intensive monitoring group. All patients will receive 5 sleep studies in their homes over the course of 6 months, as well as lung function and quality of life testing. This study is now open for patient recruitment.

Finally, we are investigating the immediate effect of using NIV on the function of the diaphragm and other breathing muscles. Patients with ALS who are advised to begin NIV by their doctors are asked to come to our Sleep Center for half a day, during which lung function testing is performed before and after two different levels of NIV. This study also offers patients the opportunity to try NIV for the first time in a completely monitored setting and have a mask fitted by expert sleep technicians and physicians. This study is also now open for patient recruitment.

Through these studies and others, we hope to better define the optimal use of NIV in ALS. While these are research studies and are not designed to offer personal benefit to study participants, we believe that many of our patients have derived real benefit from participating in these trials. If you are successfully using NIV or if you have been advised to start NIV, please consider being part of this very exciting and important work.

Amy Atkeson, MD  
Division of Pulmonary, Allergy and Critical Care Medicine  
Columbia University Medical Center



Eleanor and Lou Gehrig MDA/ALS  
Research Center:  
MDA/ALS Education Support Groups

The Muscular Dystrophy Association offers a free support group in Manhattan for individuals and their families affected by ALS. “MDA Support Groups are very important. They offer people affected with ALS a level of understanding and encouragement they can receive only from others in the same situation,” said one of the group’s participants. “The professionally facilitated groups provide an environment where people are able to share tears, frustration, support and helpful information.”

Location:

All Souls Unitarian Church  
1157 Lexington Avenue (between 79th & 80th Streets), NYC 10021  
Last Monday of every month (please call to confirm meeting date)

Time: 6-8 p.m.

MDA support groups are funded in part by proceeds raised during the Jerry Lewis Labor Day Telethon, broadcast locally on WWOR-TV MY9. Individuals who plan to attend an MDA support group are encouraged to contact Jenny Greene, ALS Health Care Services Coordinator, at [jgreene@mdausa.org](mailto:jgreene@mdausa.org) or (212) 689-9040.



For those without easy access to Manhattan, please feel free to visit educational support groups in Northern New Jersey or Westchester. See below for details:

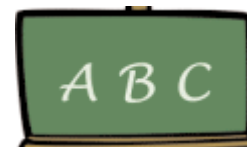
Northern New Jersey

Jewish Community Center  
on the Palisades  
411 E. Clinton Avenue  
Tenafly, NJ 07670

Please join us:

Third Thursday of each month  
4-5:30 PM

For more information contact:  
Maywood Center: 201-843-4452



Westchester

Burke Rehab Center  
(Clock Tower Bldg, Rm 202)  
785 Mamaroneck Ave  
White Plains, NY

Please join us:

Second Thursday of each month.  
6-8pm

For more information contact:  
Gloria English: 914-345-5062





Exercise Prescription for people with ALS

by Ronit Gorelik

It seems almost every week a new article or news segment focuses on yet another benefit of exercise. Ranging from preventing breast cancer to reducing the risk for Alzheimer's disease to preventing falls for the elderly, exercise has become preventative medicine's number one recommendation.

With muscle weakness, muscle atrophy, and decreased endurance, the common symptoms and signs of ALS, exercise would appear to be the treatment of choice. However, exercise and ALS share a controversial relationship. Research and evidence are lacking and little is known of the physiological response to exercise in people with ALS. Additionally, many physicians and therapists suggest that people with ALS avoid physical activity for fear of overworking and causing increasing damage to an already weakened muscle. During each weekly clinic, when the question is inevitably posed, "Should I be exercising?" it is a struggle to provide the best answer.

Exercise is hypothesized to be beneficial to those with ALS based on knowledge of how exercise affects healthy people. For example, it is known that exercise increases the capacity of major antioxidant enzymes, combats muscle atrophy, and increases mitochondrial capacity in skeletal muscle. Whether or not people with ALS have the same response as those who do not have the disease is not known.

Few studies have been performed to determine what the effect of exercise is at the onset and duration of ALS or the overall benefits or detriments of exercise for people with ALS. Recent experiments in ALS mouse models have shown that intensity of exercise may show different results – with moderate intensity exercise having a beneficial effect and high intensity having a harmful effect in comparison to sedentary controls. In recent human experiments, a trend towards less disability was observed in those people with ALS who exercised. Contradictory data has been reported regarding exercise-induced neuroprotection and the molecular mechanism of such are unknown.

Exercise can be beneficial even without directly affecting the course of the disease. The weakness caused by ALS leads to patients becoming deconditioned, resulting in compounded disability. Exercise can combat this cause of weakness and thereby delay the onset and severity of disability. Additionally, early strengthening exercise can bolster initial strength in thus far unaffected muscles so that further weakening will take longer to cause disability. Overall deconditioning can lead to secondary complications such as loss of range of motion and eventual pain. In a disease that is inherently pain-free, limiting this secondary symptom is of utmost importance. Additionally, exercise has positive effects on mood, sleep, and appetite – all of which can be greatly affected by ALS.

As with any treatment, exercise must be individually prescribed depending on level of weakness, respiratory involvement, balance, risk of falls, and personal preference. Your response to exercise should be monitored carefully. Exercise should not be performed to the point that it causes excessive fatigue, a decrease in function, an increase in respiratory symptoms or the frequency of falls. If any of these or other negative results of exercise occur, exercise intensity should be reduced and the exercise prescription should be reevaluated.

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# The Eleanor and Lou Gehrig MDA/ALS Research Center

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	Aerobic	Stretching	Strengthening
Intensity	Based on tolerance to activity	Throughout a pain-free range of motion.	Moderate intensity – use a weight you can lift 20 times and perform 2-3 sets of 10 repetitions
Duration	Based on tolerance to activity	Hold each stretch for 20-30 seconds.	Based on tolerance to activity
Type	Stationary bike, walking, swimming, water aerobics etc.	General stretching and range of motion exercises for most joints	Free weights, weight machines, resistance bands, body weight
Frequency	3-5x/week or to tolerance	Daily or multiple times a day if you experience spasticity	2-3x/week or to tolerance



Your Eleanor and Lou Gehrig MDA/ALS Center Staff

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*Special thanks to the MDA/ALS Division for their continuing support of our patients and their caregivers.*

## 4th Annual ALS Softball Tournament to "Strike out ALS"

August 1, 2009 at 7:30 AM at Glover Field-Pelham, New York

For further information, contact Joe at 914-804-2926

All proceeds are being donated to our ALS Center.

The Eleanor and Lou Gehrig MDA/ALS Research Center of Columbia University Medical Center gratefully acknowledges the patients and families who have contributed financially to the publication of the ALS Newsletter.

